Breakthrough Infection and Death after COVID-19 Vaccination: A Physics Perspective

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ABSTRACT

The largest universal immunization in history has occurred as a result of the COVID-19 pandemic. The developed COVID-19 vaccines have been shown to provide protection against severe forms of COVID-19 by inducing anti-spike neutralizing antibodies. It has been found that individuals who have not been vaccinated against COVID-19 were more likely to contract the virus during a period when the Delta variant was dominant, as compared to those who have received the complete dose of the vaccine, irrespective of the variant. However, there is no notable disparity in the likelihood of hospitalization, requirement for mechanical ventilation, or mortality between the two groups once infected. Nevertheless, those who are unvaccinated may require additional oxygen support. There are reports indicating unfavorable health effects, ranging from transient thyroid dysfunction to death following vaccination. In addition, some people are susceptible to SARS-CoV-2 infection despite they have immunized with the COVID-19 vaccine. Given all these considerations, several key factors should be better understood and considered to enable us to even more successfully manage future pandemics breakthrough infections. The effectiveness of physical treatment methods, e.g., Low Dose Radiation Therapy (LDRT) should be compared to pharmacological treatments.

Keywords

COVID-19; SARS-CoV-2; Vaccines; Cytokine Storm; Medical Physics

Introduction

The safety and effectiveness of mRNA-based, viral vector-based, and inactivated vaccines for universal vaccination against COVID-19 have been verified by the World Health Organization (WHO) [1, 2]. As of August 12, 2022, over 12.3 billion vaccine doses have been administered worldwide [3]. COVID-19 vaccines can protect against severe forms of the disease by producing anti-spike (S) neutralizing antibodies [4]. However, some individuals have reported various side effects, including thyroid, neurologic, cutaneous, and hematologic disorders after receiving the vaccine [5-7]. Although several molecular mechanisms have been proposed for these side effects [5], the exact cause is still unknown and requires further investigation. It is important to note that reports of side effects after vaccination do not necessarily indicate causality. To better understand the subject, further prospective

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longitudinal studies using control groups are needed as the world continues its largest universal immunization effort.

The occurrence of some cases of breakthrough infection, hospitalizations, and deaths were reported after COVID-19 vaccination [8]. A cohort study conducted in Iran revealed that the incidence rates of COVID-19, hospitalization, and death following vaccination were 528.2, 55.8, and 4.1 per 1,000,000 person-days, respectively [8]. Another study conducted in India on vaccinated individuals showed that breakthrough infections occurred in 7.91% of cases, with older individuals (≥61 years) and males being at higher risk [9]. Before the commencement of mass vaccination, the primary factors that posed a high risk for severe COVID-19 were recognized to be old age, diabetes, cardiovascular disease, chronic respiratory diseases, obesity, being male, kidney diseases, hematological malignancy, organ transplantation, mental disability, as well as liver, neurological, or autoimmune diseases [10]. These same risk factors may contribute to contracting COVID-19 after vaccination.

Numerous factors can influence the body's response to vaccines, including inherent characteristics like age, gender, genetics, and existing health conditions, as well as external factors like immune status, microbiota, infections, and medication use. Lifestyle and behavioral factors like smoking, alcohol consumption, physical activity, and sleep patterns, as well as nutritional factors like body mass index and micronutrient levels, can also play a role. Additionally, the type of vaccine, its dosage, adjuvant, and administration schedule, site, route, and timing, as well as any co-administered drugs, can affect the vaccine's efficacy [11]. However, the precise impact of these factors on the development of protective antibodies against SARS-CoV-2 is not yet fully understood.

The results of the Iranian cohort study showed that the AZD1222 Vaxzevria vaccine was most effective in preventing COVID-19 cases, hospitalizations, and deaths. Inactivated vaccines (using Vero Cell) had the lowest effectiveness. Diabetes and respiratory, cardiac, and renal diseases as well as neurological and mental disorders were associated with a higher risk of contracting COVID-19 after vaccination [8]. According to a study conducted in France, the likelihood of being hospitalized due to COVID-19 increases gradually with age, with the 85-89-year age group being four times more at risk than the group aged 45-54 years [12]. Likewise, the likelihood of mortality while in the hospital rises considerably with advancing age, as those between the ages of 85 and 89 face a 38-fold increase in risk compared to those aged 45 to 54. Additionally, people who have compromised immune systems and have received vaccinations, or who suffer from particular comorbidities such as lung and liver ailments, chronic kidney failure, diabetes, cardiovascular illnesses, or neurological disorders, are at a greater risk of experiencing severe cases of COVID-19 [12].

Individuals who have cancer are more susceptible to being hospitalized and experiencing mortality after contracting SARS-CoV-2 [13]. In addition, cancer patients have a higher likelihood of experiencing breakthrough infections of SARS-CoV-2 since the efficacy of vaccines is lower in this cohort compared to the control population [14]. Administering oral corticosteroids on a long-term basis may result in potential immunosuppression, thereby elevating the likelihood of contracting COVID-19 [12]. Consequently, an insufficient antibody response can escalate the occurrence of COVID-19 cases, hospitalizations, and fatalities following COVID-19 vaccination. The prior SARS-CoV-2 infection remarkably decreases the risk of breakthrough infection [15]. When the time after vaccination increases, the titer of specific antibodies decreases. Therefore, when the antibody titer falls below the protective threshold, the risk of contracting COVID-19 increases. The determination of the protection duration after primary

vaccination against COVID-19 is important to implement booster vaccination and extend protection. Moreover, the potency of vaccines may diminish as fresh strains of the virus develop. When the delta variant prevailed between August and November 2021, the occurrence of COVID-19 infections among fully vaccinated individuals in the US population was roughly 100 cases per 100,000. Moreover, some breakthrough infections can be attributed to viral-related factors, such as variants, virus transmissibility, infection load, incubation period, pathogenicity, and virus immune evasion [16]. It has been reported that the serum samples from vaccinated persons displayed 3-15, 1.4-3, and 25-40 fold reduction in antibody neutralizing capability against Beta, Delta, and Omicron variants, respectively compared to those of the earlier variants of SARS-CoV-2 [16]. As the S protein of Omicron variants (BA.1, BA.2, BA.4, and BA.5) is different than that of the wild-type virus, the antibody neutralizing capability against Omicron variants is lower in individuals who were vaccinated with WT-based vaccines [17]. The COVID-19 epidemic curve also can influence breakthrough infections.

Cumulative evidence indicates that the risk of severe infection and COVID-19-related mortality is substantially lower in vaccinated individuals compared to unvaccinated people. Although there are concerns about the potential negative effects of vaccination on the virus and on health, studies have shown that vaccination against SARS-CoV-2 can reduce the risk of death by 34% and the risk of contracting COVID-19 by 15%, compared to those who are unvaccinated [18]. A systematic review and meta-analysis has also found that during a period dominated by the Delta variant, unvaccinated individuals are at a higher risk of contracting the virus than those who are fully vaccinated, regardless of the variant. However, there were no significant differences in the likelihood of hospitalization, mechanical ventilation, or mortality after infection. Nonetheless, unvaccinated individuals had a higher need for oxygen supplementation [19]. To effectively manage breakthrough infections, it is important to consider various crucial factors.

The Risk of Death after Vaccination

Despite the inevitable crucial role of the rapid development of COVID-19 vaccines in the effective management of the pandemic, there are reports indicating adverse health effects ranging from transient thyroid dysfunction [5] to death [20] following vaccination. Two years after COVID-19 became a pandemic crisis, the mechanisms behind the major adverse health effects remain poorly understood. Recently, a group of Japanese researchers, headed by Murata [20], reported four instances of death occurring after the second dose of the COVID-19 vaccine. Despite conducting an autopsy, the cause of death could not be determined. The team discovered that vaccination led to the upregulation of 399 genes, particularly those involved in neutrophil degranulation and cytokine signaling, while 154 genes were downregulated. Based on their findings, they concluded that vaccination could result in immune dysregulation, specifically a cytokine storm [20].

According to a previous study by Jafarzadeh et al. [5], although there is a small chance of rare side effects such as temporary thyroid issues, getting vaccinated has a positive impact on ending the pandemic and decreasing mortality rates. Recent death reports do not seem to be able to change the existence of a net benefit for vaccination. However, we need to first assess if the observed death events are truly related to vaccination or just show a random coincidence. When we consider the total number of vaccine doses used in Japan, 4 death cases after vaccination can be a random coincidence. If the coincidence is ruled out, then we should investigate what potential mechanisms may be involved in these death events. Figure 1 shows some of the most likely mechanisms behind the post-vaccination death reports.

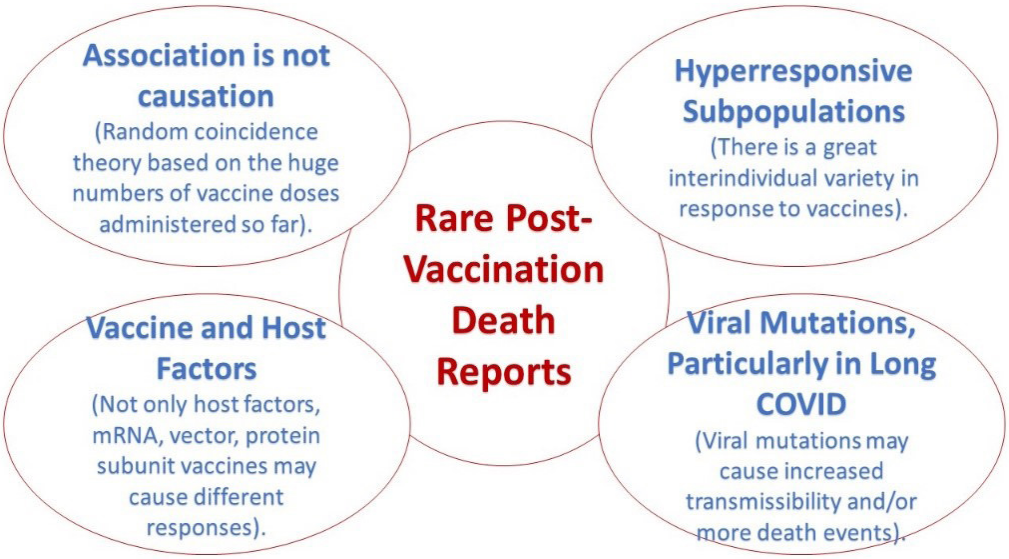

Figure 1: Different theories about the rare post-vaccination death reports

The Virus is to stay

There is a growing body of evidence indicating that SARS-CoV-2 will not be eradicated and will continue to spread among humans. Some scientists predict that future generations will develop greater resistance to COVID-19, resulting in a reduced risk of severe illness. Oberemok et al. have expressed a similar view in their article SARS-CoV-2 will persist in the human population: an opinion from the point of view of the virus-host relationship" published in Inflammation Research, stating that the virus will persist in the human population [21]. They believe that the virus will eventually lead to a more resilient population, particularly among individuals of reproductive age, despite the fatalities caused by it. The authors have also highlighted the impossibility of preventing the virus from generating new strains and posing a threat to the world with new pandemics due to natural genetic mechanisms of mutations and recombination [21]. Bevelacqua and Mortazavi have noted that the issue may be much more complex than natural selection [22]. As less-efficient vaccines and antiviral drugs might drive the virus to evolutionary processes [23], the adverse outcomes of exerting selective pressure by the advent of vaccines or new therapies should carefully be considered [24]. A report in the prestigious journal Science from three years ago noted that as the virus spreads through people who have not been exposed to it before, there may not be much pressure for it to evolve. However, the introduction of vaccines or new treatments could change this and force the virus to adapt and evolve [24]. The transmission of SARS-CoV-2 is affected by various factors such as the host's immune response, viral replication, and mutation rate [25].

A Physics Perspective: Low-Dose Radiation Therapy Can Change the Game

Physical principles were the basis of many guidelines in the prevention of COVID-19 spreading. For example, the advantage of the Earth's gravity was the basis of social distancing. Given this, it has been discussed that COVID-19 fatality in space might be significantly higher than that on Earth [26]. However as the pendulum of COVID-19 science has been always swinging, The US CDC released new guidance for the national response to COV-

ID-19 on Aug 11, 2022. The revised guidance puts less emphasis on social distancing and removes quarantine requirements for exposure to the virus, places less emphasis on screening those without symptoms, and updates COVID-19 protocols in schools. The Washington Post has called the new guideline a strategic shift "CDC loosens coronavirus guidance, signaling strategic shift". Moreover, CDC has accepted that SARS-CoV-2 is here to stay "We know that Covid-19 is here to stay," said Greta Massetti, an epidemiologist at CDC.

Moving to the therapeutic applications of physics, Low Dose Radiation Therapy (LDRT) has been shown to lower death rates in individuals with bacterial and viral-related pneumonia [27]. Uncontrolled Inflammatory responses as well as cytokine storms are the key players in the pathogenesis of COVID-19 [10, 28]. In early April 2020, the first proposal for using LDRT to treat COVID-19-associated pneumonia was made. However, X-ray therapy has been used to treat pneumonia since the pre-antibiotic era of the twentieth century, although its effectiveness is uncertain. In a 2013 review by Calabrese and Dhavan [29], 15 reports were presented, covering 863 patients with severe pneumonia caused by various pathogens. LDRT affects leukocytes, endothelial cells, and fibroblasts, as well as the production of cytokines and chemokines, in order to regulate inflammation [27, 30, 31]. LDRT may enhance antiviral immune responses by increasing Natural Killer (NK) and CD8+ T-cell-dependent activity, as well as IFN-γ generation [32, 33]. Given this consideration, two years after the pandemic, it seems that physical treatment methods can compete with pharmacological treatments. Regarding reinfection, more studies are needed to answer the key question of whether physical treatment methods such as LDRT can decrease the rates of serious reinfection and death after receiving the 2nd or booster doses of COVID-19 vaccines.

Conclusion

The COVID-19 pandemic has resulted in the largest global immunization effort in history. While the overall outcome of the vaccination has been positive and has saved many lives, there have been reports of negative health effects and even deaths. Therefore, it is crucial to comprehend the factors that trigger adverse health effects to effectively manage future breakthrough infections. Although there are indications that future generations will be more resistant to COVID-19 and the risk of severe illness will decrease over time, it is essential to understand how lifestyle and behavioral factors, such as smoking, alcohol consumption, physical activity, and sleep, and nutritional factors like body mass index and micronutrients, affect the outcome. Additionally, the effects of various vaccine factors, including vaccine type, product, adjuvant, dose, and administration factors such as schedule, site, route, time of vaccination, and co-administered drugs, should be evaluated to enhance treatment methods during future pandemics. Furthermore, the potential effectiveness of physical treatment methods like Low Dose Radiation Therapy (LDRT) should be compared to pharmacological treatments.

Authors' Contribution

SAR. Mortazavi, SMJ. Mortazavi and L. Sihver conceived the idea. SAR. Mortazavi drafted the manuscript. A. Jafarzadeh, SMJ. Mortazavi, L Sihver, and A. Ghadimi-Moghadam supervised the revision of the manuscript and reviewed the comments and edits of other members of the team. All the authors read, revised, and approved the final version of the manuscript, which was submitted by L. Sihver.

Conflict of Interest

None

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